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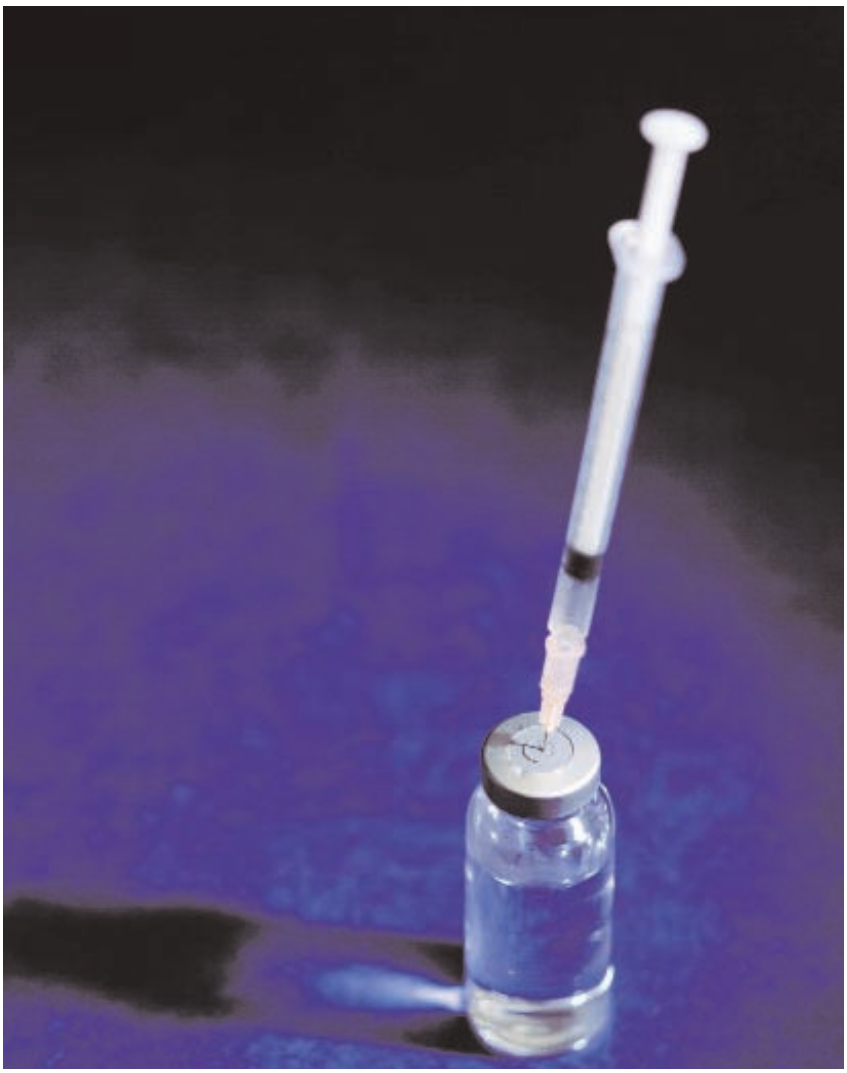
Long-Acting Risperidone in the Treatment of Schizophrenia: *An Evidence-Based Approach*

INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by positive and negative symptoms. The course of the illness is punctuated by relapses and remissions. Treatment of schizophrenia usually requires long-term maintainence treatment with antipsychotics, which is complicated by high rates of nonadherence.[1]

Long-acting formulations of antipsychotics were introduced in the 1960s, and they have the advantages of avoidance of first-pass metabolism and assured medication delivery, hence stabilization of serum drug levels.[2] Depot antipsychotics have been found to be well tolerated and more efficacious than oral medications.[3] They also provide lower steady state therapeutic drug concentrations compared to the widely fluctuating concentrations seen with oral medications,[4] and this has been associated with a lower propensity to produce side effects.

Risperidone is a potent serotonin 5HT2A and dopamine D2 antagonist. It also blocks alpha-1 adrenergic and dopamine D4 receptors and has moderate affinity for histamine H1 and alpha-2 adrenergic receptors, weak affinity for serotonin 5HT1A and little or



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no affinity for muscarinic M1 receptor.[5]

In addition to improvement of positive symptoms of schizophrenia through dopamine antagonism, risperidone also improves negative symptoms of schizophrenia and reduces the risk of extrapyramidal side effects through serotonergic antagonism.

A D2 receptor occupancy rate of 60 to 65 percent is necessary for antipsychotic activity, and extrapyramidal side effects (EPSE) are most likely when D2 receptor occupancy exceeds 80 percent.[6]

The long-acting formulation of risperidone (LA risperidone) is an aqueous suspension of microspheres, each of which is a small bead consisting of a matrix of risperidone and a carbohydrate-based biodegradable polymer. The microspheres are gradually hydrolysed at the injection site, providing a sustained and predictable release of risperidone. Significant release of the drug begins three weeks after the first injection and is maintained through Weeks 4 to 6. Therapeutic plasma concentrations are reached 3 to 4 weeks after the first injection.[7] Hence oral supplementation should be given for the first three weeks of treatment with LA risperidone to maintain therapeutic concentrations until the main release of risperidone from the injection site has begun.

DOSAGE

Patients who have never taken oral risperidone should be given a hypersensitivity challenge with 1- to 2mg per day of oral risperidone for two consecutive days before starting LA risperidone. The recommended dose is 25mg every two weeks. The dose for patients not responding can be increased to 37.5mg or 50mg every two weeks, but increases should not be made more frequently than every four weeks. The clinical effects of dose adjustments should not be anticipated earlier than three weeks after the last injection at the increased dose.[8]

LA risperidone was approved for use in the United States in October, 2003. It had previously been licensed for use in 40 countries.

What is the evidence that LA risperidone works? Is it superior to oral and other injectible depot antipsychotics? Can patients stabilized on other antipsychotics be switched to LA risperidone? Do patients tolerate this drug well?

We attempted to answer these questions by looking at the available evidence. We searched the literature using MEDLINE, EMBASE, and PSYCHLIT for all studies about LA risperidone. We also contacted contacted Janssen Pharmaceuticals for all unpublished data on file.

THE QUESTION: Has LA risperidone been shown to be efficacious in the treatment of patients with schizophrenia?

Results: The most compelling evidence to answer this question is the study by John Kane, et al.,[9] which was a 12-week multisite, randomized, double-blind, parallel group study in the US with 370 patients randomized to receive either 25mg, 50mg, or 75mg of LA risperidone or placebo every two weeks. Patients were rated on baseline to end point on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI). LA risperidone was effective in multiple symptom domains. They concluded that LA risperidone was well tolerated and efficacious with response to positive and negative symptoms. Twenty-five milligrams of risperidone every two weeks offered the optimum risk benefit ratio for most patients.

Fleischacker, et al.,[10] in a 12-month, open-label trial in Europe and Canada, studied 615 patients who had been stable either on oral or depot antipsychotics. Patients were treated with 25mg, 50mg, or 75mg of risperidone. Improvement in severity was documented in each group with significant improvement in PANSS. Patients in the 75mg group were less responsive than the other two groups.

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THE QUESTION: How well do patients tolerate LA risperidone?

Results: LA risperidone appears to be well tolerated. In the 12-week, double-blind study,[9] incidence of extrapyramidal side effects (EPSE) in the 25mg group were comparable to that of placebo. The occurrence of EPSE was

Nasrallah, et al., found that **patients receiving LA risperidone showed improvement in health-related quality of life scores toward normal levels.**

Paton and Okocha concluded that **supplementation with oral antipsychotics may be required for more than three months** *and that more than six months may be required to identify all responders.*

mild at baseline and did not change during the trial.

In the 12-month study,[10] EPSE decreased in each of the groups during the 12 months of study. The common adverse effects reported were anxiety (24%), insomnia (21%), depression (14%), and headaches (12%).

Discontinuation rates were low in both the studies, and injection site pain was generally mild in both trials.

THE QUESTION: Can patients stable on other medications be switched safely to LA risperidone? Are there any added benefits of this switch?

Results: Chue, et al.,[11] in a double-blind, multicenter trial conducted across 95 sites in the UK, Europe, North America, and Africa, studied 640 patients with schizophrenia who received oral risperidone for eight weeks, following which patients were randomly assigned to receive LA risperidone or continued oral risperidone for 12 weeks. No greater benefit was seen with LA risperidone than with oral risperidone.

Vauth, et al.,[12] switched 119 patients previously stabilized on oral antipsychotics, mainly risperidone in a six-month study. Significant improvements in symptom control were achieved, even though the patients had been regarded as stable at study entry. Significant improvements were noted on the PANSS, CGI, and Global Assessment of Functioning (GAF) with a greater proportion of patients reporting satisfaction at end point than at baseline.

Lindenmayer, et al.,[13] in a 12-week, multicenter, exploratory, open-label trial in the US, switched patients from oral treatment with haloperidol, quetiapine, or olanzapine. Patients were given 25mg, 50mg, or 75mg of LA risperidone. Overall symptom improvements in the PANSS were seen in each of the three patient groups, with significant improvements at Weeks 8 and 12.

Turner, et al.,[14] switched 166 patients on conventional depot antipsychotics to LA risperidone. In this 12-week, open-label, multicenter trial scores on the PANSS and CGI were significantly reduced during treatment with 48 percent showing further symptom improvement with minimal movement disorders.

THE QUESTION: Does LA risperidone work in the long term?

Results: Kushner, et al.,[16] attempted to document the long-term safety and tolerability of LA risperidone. Patients were followed up for a period of four years following a double-blind study. They found a reduction in CGI scores in patients receiving LA risperidone, whereas patients who had received placebo had an increase in the mean CGI scores, which were reduced when they received risperidone.

THE QUESTION: Does the use of LA risperidone result in cost savings and improved quality of life?

Results: Leal, et al.,[17] in Europe studied healthcare resource utilization during treatment with LA risperidone in 397 patients. The number of patients needing hospitalization, partial hospitalization, and outpatient consultations decreased significantly.

Eriksson, et al., in Sweden,[18] conducted an health economic analysis with regards to need for institutional care before and during treatment with LA risperidone. They showed that a switch to LA risperidone reduces the number and duration of institutional psychiatric care episodes in patients with schizophrenia, which results in overall cost savings associated with schizophrenia.

Nasrallah, et al.,[19] found that patients receiving LA risperidone showed improvement in health-related quality of life scores towards normal levels.

THE QUESTION: How have the results obtained in clinical trials been translated to real world practice?

Results: Two naturalistic studies of the experience of the use of LA risperidone have been published, both from the United Kingdom.

Taylor and colleagues from London followed up patients who were prescribed LA risperidone for a period of six months in a naturalistic setting. They found overall that 51 percent of the sub-

jects discontinued the medications, and the main reason was lack of effect. However, 61 percent of the subjects showed improvement in CGI scores between baseline and endpoint, with antipsychotic coprescriptions (i.e., prescriptions of other antipsychotics in conjunction with LA risperidone) reduced from 71 percent of subjects in the beginning to eight percent at endpoint.[20]

Paton and Okocha followed up 50 patients in England on LA risperidone.[21] The majority of patients had a history of nonadherence with oral medication. They found that 40 percent of the patients had achieved good or very good clinical outcomes at six months. Eighteen percent fared poorly, and 24 percent were switched to other treatments. They concluded that supplementation with oral antipsychotics may be required for more than three months and that more than six months may be required to identify all responders.

CRITICAL EVALUATION

Most of the studies reported in this article were open-label trials with the exception of the studies by Kane, et al.,[9] and Chue, et al.[11] All of the studies also excluded patients with substance abuse, which is highly comorbid in patients with schizophrenia and which may contribute to nonadherence and relapse. The studies also excluded patients with tardive dyskinesia and history of neuroleptic malignant syndrome, so it is not surprising that the rates of extrapyramidal side effects noted were low. Some of the studies also excluded patients unresponsive to risperidone, which again can artificially inflate the efficacy rates. The length of the study by Kane, et al.,[9] at 12 weeks is too short to determine if the positive effects obtained can be maintained over the longer term and, also as Paton, et al.[21] suggest, may be too short to identify all responders. All of the studies have been funded by or the authors had affiliations to Janssen, the makers of LA Risperdal (risperidone).

CONCLUSIONS

LA risperidone offers the combined benefits of an atypical antipsychotic along with the assurance of a long-acting formulation. It has been shown to be efficacious, well tolerated, and as having minimal side effects. Not only do patients with adherence problems benefit from this new formulation, but patients who are stable on other medications benefit as well. Properly used, LA risperidone has the potential to reduce relapses that patients with schizophrenia experience.

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